Challenges in the treatment of febrile neutropenia

S229 Choice of therapy according to prognostic factors and cost issues

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Febrile neutropenia (FN) is a changing syndrome which requires periodic updates as our armamentarium against this condition improves and the characteristics of the pathogens change. In addition, cost of therapy has become a major issue when designing therapeutic strategies. The treatment of FN has changed over the past 20 years and is still constantly being re-evaluated in relation to modifications of the nature of the offending pathogens, availability of new drugs for treatment of infections, and changes in the types of patient who become neutropenic as a consequence of cytostatic therapy. The present review will deal with recommendations for the treatment of FN, with special attention to its cost benefit, and will be based on the results of the recently published IATCG-EORTC trials. Costs will be evaluated on the basis of the daily expenses for medical care of FN in Belgium as they are presently charged to the social security services. On the basis of the preceding considerations, an algorithm for the treatment of FN that takes into consideration the cost benefit will be proposed as an incentive to further clinical studies aimed at its validation or rejection. It is recognized, however, that further economic analyses should also be based on real-life studies (not necessarily on well-controlled, randomized and blinded trials). This is relevant for policy-makers.

S230 Rational modifications of empirical therapy in febrile neutropenia

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Empirical broad-spectrum antibiotic therapy has become a generally accepted strategy in the treatment of febrile neutropenic patients. Particularly in patients with prolonged neutropenia, subsequent adaptation of such a regimen will be the rule rather than the exception. Since there are no uniformly accepted guidelines for the modification of antibiotic therapy during the post-empirical phase, we assessed the impact of a set of rules that evolved during the conduction of the first randomized trials. Evaluation of the clinician's compliance with these rules in 1951 febrile neutropenic episodes was the subject of the present analysis. Treatment was modified in 761 (39%) cases and these changes were made according the rules in 76%. For 75% of the alterations in treatment during the evening and night shifts, no reasonable explanation could be established, while 93% of the modifications during the normal working hours were made for objective reasons. The empirical regimen was more frequently changed in patients with a clinical focus of infection at the onset of fever in comparison with patients who showed fever as the only symptom of a possible infection. The perceived need for modification amounted to 69% in pulmonary infections, to 51% in skin and soft tissue infections, to 44% in patients with abdominal complaints, and to 37% in the upper respiratory tract infections. Glycopeptides constituted 22% of modifications, particularly in patients with a central venous catheter, and systemically active antifungals were administered in 16% of cases. Especially inexperienced clinicians tend to adjust antibiotic therapy in spite of the fact that persistence of fever alone seldom reflects inadequate treatment when the clinical condition of the patient is stable or improving. On the other hand, the development of subsequent infectious events emphasizes that a genuine need for modification does frequently exist.

S231 Indications for bone marrow-stimulating or -protecting agents

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The curative potential of intensive antineoplastic chemotherapy is limited by treatment- induced toxicity, predominantly by severe and prolonged myelosuppression as well as mucosal damage, both resulting in serious and life-threatening infections. The advent of recombinant hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF) and, recently, also stem cell factor (SCF), interleukin-3, interleukin-11 and thrombopoietin (TPO) or megakaryocyte growth and development factor (MGDF) has opened new perspectives for a marked reduction of chemotherapy-induced neutropenia and thrombopenia. Prospective, randomized clinical trials have demonstrated a significant decrease in the incidence of infections as well as a shortening of hospitalization by prophylactic administration of G-CSF or GM-CSF post-chemotherapy, and this prophylactic use is recommended in patients in whom febrile complications during neutropenia are expected with more than 40% probability. In patients with serious life-threatening infections who are not receiving G-CSF or GM-CSF prophylactically, interventional application may be useful in individual cases. The thiophosphate prodrug amifostine may reduce mucosal and bone marrow toxicity from chemo/radiotherapy and has shown some clinical benefit in solid tumor patients without significant impairment of anticancer treatment efficacy. Its usefulness in patients with high-grade malignant hematologic diseases, however, has not been demonstrated so far.

S232 Costs and benefits of various approaches to the febrile neutropenic patient

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The strategies for cost containment in the management of febrile neutropenia are represented by the control of the severity and duration of neutropenia with colony-stimulating factors, the reduction of the hospitalization period with home or ambulatory care, and the choice of the most cost-effective empirical antibiotic regimen. Several alternatives to hospital-based therapy have been evaluated in low-risk neutropenic patients: early discharge to home antibiotic therapy or treatment of the entire febrile episode with intravenous or oral antibiotics in the ambulatory setting or at home. Monotherapy (i.e. oral fluoroquinolones, once-daily third-generation cephalosporins) can be used, depending on local epidemiology. The approach to high-risk neutropenic patients is represented by hospitalization and prompt institution of empirical antibiotic therapy. Cost-efficacy analysis should be planned to prospectively identify the most effective and less costly regimen. Cost-minimization analysis is able to compare the costs of two equally effective regimens. The elements useful for evaluating the economic impact of the empirical antibiotic regimens are represented by the cost of therapy (drug acquisition cost and administration cost, including nursing time and the materials), the cost of failure and the cost of the adverse events (drug acquisition cost, administration cost and cost of diagnostic evaluation). The comparative analysis of the acquisition cost of several empirical antibiotic regimens validated in RCT indicates that

the combination of ceftriaxone and amikacin is less costly than ceftazidime plus amikacin, piperacillin/tazobactam plus amikacin, and meropenem. However, it should be stressed that the choice of antibiotic regimen should be based primarily on clinical and epidemiologic considerations; that is, in a setting of high risk of *Pseudomonas aeruginosa* infections, an antipseudomonal beta-lactam antibiotic should be preferred.

New aspects of cystic fibrosis, lung infection and inflammation

S239 Defensins in cystic fibrosis (CF)

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Because *Pseudomonas aeruginosa* represents an imminent threat to patients with CF but not healthy persons, we addressed the question what keeps normal lungs free of *P. aeruginosa* infection. Based on the working hypothesis that lung epithelial cells secrete *P. aeruginosa* killing peptide antibiotics, we isolated from supernatants of *P. aeruginosa*-stimulated lung epithelium cell line U549 a 4-kDa *P. aeruginosa* killing peptide, which is identical to human ß-defensin 2 (hBD-2), a defensin we recently discovered in inflamed skin. Natural hBD-2 strongly killed *P. aeruginosa* (LD_{90}:10 mg/L), but not *Staphylococcus aureus* (growth inhibition at concentration 100 mg/L). In contrast to all known human defensins, hBD-2 synthesis is inducible in epithelial cells by contact with bacteria or pro-inflammatory cytokines, which is supported by analyses of the promoter region of the hBD-2 gene. Because in CF it is believed that increased NaCl concentrations may affect antimicrobial activity of endogenous peptide antibiotics, we investigated the salt sensitivity of hBD-2 and found a dose-dependent inhibition of *P. aeruginosa* killing activity (IC_{50}: ~80 mM), indicating that hBD-2 is salt sensitive at physiologic ion strength. Investigation for hBD-2 in sputum of CF patients revealed immunoreactive hBD-2, indicating that hBD-2 production is not defective in CF. Systematic screening of CF patients' sputum for antimicrobial activity, however, revealed—apart from known defensins 1–3 and lysozyme—a number of as yet not identified molecules that might be important in antimicrobial defense in CF.

S240 Epithelial cell interactions involving CFTR and bacterial pathogens

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The CF transmembrane conductance regulator (CFTR) plays a critical role as a receptor involved in the lung's response to *Pseudomonas aeruginosa*. The absence of CFTR protein in most severe cases of CF results in decreased clearance of *P. aeruginosa* from the lung in the early stages of infection. We have recently determined that under the right conditions CF mice are hypersusceptible to oropharyngeal colonization by *P. aeruginosa* from environmental sources as well as experimentally induced *P. aeruginosa* lung infection. All mice exposed to *P. aeruginosa* in drinking water become colonized in the oropharynx, but once the contaminated water is removed, both wild-type and heterozygote *F508 Cftr mice clear the colonization, whereas CF mice remain colonized for prolonged periods. Introduction of *P. aeruginosa* enmeshed in alginate beads into the lungs of CF mice results in long-term infection accompanied by significant changes in pulmonary obstruction, whereas mice with at least one wild-type Cftr gene clear this infection. CFTR is also utilized by *Salmonella typhi* as a receptor for translocation from the gastrointestinal tract. Recent studies in CF mice with a G551 D allele indicate that this Cftr mutation results in decreased uptake of both *S. typhi* and *P. aeruginosa* by homozygote G551 D and heterozygote G551 D mice compared with wild-type mice. This is identical to results reported for *F508 Cftr mice. Overall, CFTR is an important receptor for both *P. aeruginosa* and *S. typhi*, and changes in CFTR protein due to different gene mutations can result in a similar phenotype in regard to susceptibility and resistance to *P. aeruginosa* and *S. typhi* infections.

S241 Neutrophil–parasite interactions

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Most patients with cystic fibrosis (CF) suffer from chronic endobronchial *Pseudomonas aeruginosa* infections. The lung tissue damage is caused by continuous activation of the immunologically specific inflammatory defense mechanisms of the lungs initiated by the antibody response and dominated by polymorphonuclear neutrophil leukocytes and their proteolytic and oxidative products. This inflammation induces a phenotypic shift from non-mucoid to mucoid, alginate-producing phenotypes of *P. aeruginosa* which then grow as a biofilm endobronchially. Such biofilms are impossible to eradicate with antibiotics. Currently used treatment strategies are chronic suppressive antibiotic treatment against *P. aeruginosa* and use of anti-inflammatory drugs such as inhaled budesonide or systemic treatment with ibuprofen or piroxicam. The immune response responsible for the tissue damage mimics a Th2 response, and animal experiments suggest that a shift to a Th1-like response by, for example, gamma-interferon treatment, may delay the tissue damage. Clinical trials have, however, not yet been carried out with gamma-interferon treatment.

S242 Bacterial vaccines in cystic fibrosis

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In patients with cystic fibrosis (CF), *Pseudomonas aeruginosa* and *Staphylococcus aureus* cause chronic pulmonary infections which are difficult to treat with antibiotics. Loss of lung function is the major cause of death in CF. Vaccination is a possible way to prevent these infections, and several antigens, including *P. aeruginosa* flagella and *S. aureus* exopolysaccharides, are promising vaccine candidates. In vitro and animal studies showed that flagella antigens were protective in compromised animals. Phase 1 studies using Immuno s flagella vaccines in healthy individuals and CF patients revealed that these vaccine preparations were well tolerated, showed no adverse side effects and gave rise to high and long-lasting antibody titers in the circulation of the individuals. Furthermore, immunization with a flagella vaccine elicited specific anti-flagellar antibodies not only systemically, but also in the secretory immune system of the airways. Consequently, a phase III multicenter vaccine trial using the *P. aeruginosa* 5142/1210-Flagella Vaccine IMMUNO was initiated. The study design is placebo-controlled, randomized and double-blind, involving about 500 CF patients without *P. aeruginosa* lung infection in 25 European CF centers.